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18N2/0425

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| SPECTOR | EXAMINER |
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| ART UNIT | PAPER NUMBER |
| 1812 | 4 |

DATE MAILED: 04/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice re Patent Drawing, PTO-848. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, Form PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 1-48 are pending in the application.
Of the above, claims 1-7, 28-48 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 8-27 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-48 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-848).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received
☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Part III: Detailed Office Action

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-7 and 30-32, drawn to flt3-ligand, classified in Class 530, subclasses 350 or 399.

II. Claims 8-27, drawn to DNA, vectors and host cells, classified in Class 536, subclass 23.5 and Class 435, subclasses 240.1, 320.1 and 252.3.

III. Claims 28 and 29, drawn to anti-flt3/flk2-L antibodies, classified in Class 530, subclass 387.7.

IV. Claims 33-35 and 37-45 drawn to an autologous transplantation method, a transfection method, a gene therapy method, and in vivo methods of treatment using flt3-L, classified in Class 424, subclasses 93.7 and 93.21, Class 435, subclass 172.1 and Class 514, subclass 12.

V. Claims 36, drawn to growth medium comprising flt3-L, classified in Class 435, subclass 240.3.

VI. Claim 46, drawn to transgenic mammals, classified in Class 800, subclass 2.

VII. Claims 47 and 48, drawn to a cell sorting method, classified in Class 435, subclass 7.21.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids, vectors, cells and methods of Invention II are related to the protein of Invention I by virtue of encoding/producing same. The DNA molecule has utility for the recombinant production of the protein in a host cell. Although the DNA molecule (as well as the vectors, host cells and method) and protein are related since the DNA encodes the specifically claimed protein and Invention II may collectively be used to produce the protein of Invention I, they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide synthesis or purification from the natural source. Further, the DNA may be used for processes other than the production of the protein, such as nucleic acid hybridization assay. As Inventions I and II are distinct for reasons cited herein, it

follows that the nucleic acids, vectors, cells and methods of Invention II are also distinct from the composition of Invention V, which comprises the protein of Invention I.

The nucleic acids, vectors and cells of Invention II are distinct products from the transgenic animals of Invention VI. Although the nucleic acids and some of the vectors and possibly some of the transformed cells of Invention II may be useful for the production of the transgenic animals, they are also useful for patentably distinct processes such as *in vitro* manufacture of protein, as hybridization probes, etc. The remainder of the vectors, cells and the method of Invention II are distinct from the animals of Invention VI wherein each does not require the other.

The proteins of Invention I are related to the antibodies of Invention III by virtue of being the cognate antigen, necessary for the production of the antibodies. Although the protein and antibody are related due to the necessary steric complementarity of the two, they are distinct inventions because the protein can be used in another and materially different process from the use for production of the antibody, such as in a pharmaceutical or cell growth composition in its own right, or to assay or purify the cognate receptor (as the protein is itself a ligand), or in assays for the identification of agonists or antagonists of the receptor protein.

The nucleic acids of Invention II are related to the antibodies of Invention III by virtue of encoding the protein to which the antibodies are reactive. As the DNA and protein themselves are distinct for reasons cited above, the DNA and the antibodies to the protein are also distinct; they are products which are manufactured by different processes, are not required for one another's manufacture, and are used in distinct ways.

The proteins of Invention I are related to the methods of each of Inventions IV and VII as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product as claimed may be used in either of the patentably distinct processes of Inventions IV and VII. Inventions IV and VII are themselves distinct as they are drawn to different methods of using a

single protein, which methods have different purposes, involve different process steps and endpoints, and require substantially different searches. As the methods of Inventions IV and VII are distinct from the protein of Invention I and the DNA, vectors, host cells and expression method of Invention II are similarly distinct from the protein of Invention I, the DNA, vectors, host cells and expression method of Invention II are also distinct from the methods of using the protein, that is, Inventions IV and VII.

Invention V is related to Invention I as a composition which requires the protein of Invention I. These two inventions constitute distinct products wherein whereas the growth medium of Invention V is useful for stimulating cell growth *in vitro*, the protein and pharmaceutical compositions of Invention I are useful for *in vivo* therapy as well as for the patentably distinct method of cell sorting, as evidenced by Invention VII.

Inventions I and V are *each* related to Invention VI as separate products which share in common the protein of Invention I. However, the transgenic animals of Invention VI are manufactured without the use of the protein, the protein may be produced without the transgenic animals, and the three inventions are useful for different and patentably distinct processes.

The antibodies of Invention III are unrelated to each of the methods of Inventions IV and VII, wherein the antibodies are not required for the methods, and the methods as they are claimed are not useful for the manufacture of the claimed antibodies. The antibodies of Invention III are unrelated to each of the compositions of Inventions V and VI, wherein neither composition requires the antibodies, nor is used for the manufacture of the claimed antibodies.

Inventions V, VI and VII are mutually distinct and unrelated, wherein each is not required, one for the others.

Inventions V and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the product may be used in materially different processes such as for the cultivation of cells for maintenance in tissue culture, or in a bioassay for totipotent

hematopoietic stem cells.

Inventions VI and IV are distinct and unrelated as the product of invention VI may not be made by any of the various processes of Invention IV, nor is such product necessary for any of said methods.

5 Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

10 Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

15 Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

20 During a telephone conversation with Steve Malaska on April 10, 1995 a provisional election was made without traverse to prosecute the invention of Group II, claims 8-27. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-7 and 28-48 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Formal Matters:

The disclosure is objected to because of the following informalities; Appropriate correction is required:

- 25 - Page 9, line 21 lists flt3-L as a preferred recruitment factor to be administered with flt3-L.
- Page 33, the specification discloses that vector sf HAV-EO410 containing "the flt3-L cDNA" has been deposited as ATCC number 69286. However, it is not clear from the specification what "the flt3-L cDNA" is, as two alternative splice variants have been disclosed in the paragraph

immediately preceding the deposit statement.

-The pendency status of all applications to which reference is made at page 1 of the specification should be updated.

5 Claim 12 is objected to because the word "amino" is misspelled (see part (d), line 2).
Appropriate correction is required.

10 The deposit of biological organisms is not necessary for enablement of the invention as
it is currently claimed (see 37 C.F.R. §1.808(a)). Examiner acknowledges the deposit of
organisms under accession number ATCC 69286 and 69382 under terms of the Budapest
Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent
Procedure (see the specification at pages 33 and 34). Applicants are advised that should, due
to amendment of the claims, such deposit be required for enablement, applicants must state that
all restrictions on the availability to the public of the deposited material will be irrevocably
15 removed upon the granting of a patent.

Objections/Rejections not over Prior Art:

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

20 The specification shall contain a written description of the invention, and of the manner
and process of making and using it, in such full, clear, concise, and exact terms as to
enable any person skilled in the art to which it pertains, or with which it is most nearly
connected, to make and use the same and shall set forth the best mode contemplated by
the inventor of carrying out his invention.

25 The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to
provide an adequate written description of the invention and failing to adequately teach how to
make and/or use the invention, i.e. failing to provide an enabling disclosure.

30 The specification does not present an adequate description of the invention; specifically,
what is meant by "a Flt3-L polypeptide". It is evident from the usage of this term in the
specification that it is intended to encompass species which are other than full-length flt3-L, for

example, soluble forms, truncated species, etc. However, there is no indication in the current specification as filed as to whether such flt3-L polypeptides must retain particular properties of full-length flt3-L, such as ability to bind flt3, retention of one or more epitopic regions of native flt3-L, etc. It is noted that the phrase "flt3-L polypeptide" has at least two valid interpretations, including (a) a flt3-l which is a polypeptide, or (b) a polypeptide which is a portion of a flt3-L (and may or may not have flt3 binding activity itself). Further, in the event that applicants intend the term to denote "biologically active" flt3-L polypeptides, the specification does not clearly define biological activity; at page 7¶3 of the specification, biological activity is defined as (a) the ability to bind flt3 or alternatively, (b) the ability to transduce a signal via flt3. The specification does not adequately describe how a flt3-L polypeptide would transduce a signal via flt3 without also binding to flt3.

Example 7 is not clear; the text indicates that three species of the ligand were used in the experiments, whereas it is not indicated whether the data presented in Tables 1 and 2 represent an experiment with only one of the three species (and if so, which) or whether results from all three species are represented, and whether all three species gave analogous results. Applicants are reminded in amending the specification to avoid the introduction of new matter.

Enablement of the current specification as filed is not commensurate in scope with claims to nucleic acids encoding any and all possible ligands of the flt3 receptor. The current specification enables only nucleic acids encoding a single such ligand, obtained from mouse and human cell lines, as represented by SEQ ID NO:2 or 6, or the truncated versions thereof as outlined at page 12 ¶1 of the specification. It is well known in the art that receptors may have multiple ligands, especially, as in the current case, when the receptors are expressed on numerous and divergent tissue types. It is likely that there are multiple flt3-ligands; the current specification as filed teaches how to make and use only the particularly disclosed ligand, and does not enable claims to any and all possible flt3 ligands. Further, it is noted that the current specification discloses at page 33 that there exists at least one splice variant of the disclosed ligand, but does not enable such (no sequence is disclosed, nor is there adequate information about the splice variant to enable the ordinary artisan to obtain such without undue

experimentation, as the splice variant is not sufficiently described). The mere recitation of a name, i.e. flt3-L (or biological activity thereof) to describe the claimed invention is not sufficient to satisfy the statutes' requirement of adequately describing and setting forth the inventive concept. In order to avoid possible confusion over proteins with the same or similar names that may be found to have patentably different structure and/or utility, proteins claimed by a particular name (or nucleic acids encoding such) should be further distinguished in the claims by conventional protein characterization according to known parameters, such as by molecular weight, pI, amino acid sequence information, whether the protein is a monomer or multimer, function(s) and/or activity, and/or other finger-printing techniques such as IR, NMR, or UV spectroscopy data and/or other known properties which would serve to distinguish the claimed protein from other flt3 ligands.

Enablement of the current specification as filed is not commensurate in scope with claims to DNA molecules which hybridize under moderately stringent conditions to the cDNA disclosed in the current specification or alternatively are "derived" from the coding region of the flt3-L gene, and which encode a "biologically active" flt3-L. The specification defines biological activity as either the ability to bind to the flt3 receptor or to cause the flt3 receptor to transduce a signal. Claim 12(c) is therefore drawn to DNA molecules which hybridize under moderately stringent conditions to that disclosed, and encode a protein which binds flt3. However, there has been no characterization of what portions of the protein are necessary for such binding (other than the general characterization that it is the extracellular region which is functional), nor what specific alterations may be made in the protein without loss of binding activity. Therefore, applicants have failed to adequately teach how to make the DNA molecules of claim 12(c) in a fashion commensurate in scope with the claims. With respect to claim 12(a), which recites that the DNA is "derived" from the coding region of a flt3-L gene, such language not only encompasses both silent and non-silent base substitutions, but all other possible alterations which would not destroy binding activity; the current specification as filed does not teach how to make a commensurate number of such species. See M.P.E.P. §§ 706.03(n) and 706.03(z). The examples provided in the specification do not provide a representative number of different DNA

sequences for the entire scope of the claims that would enable all of the above discussed DNA sequences with assurances that they possess or encode proteins having the desired activity. The general disclosures of (for example) what conservative substitutions are do not serve as sufficient guidance to enable the breadth of the Claims for the various DNA sequences claimed. See Ex parte Forman, 230 USPQ 546. Since the first paragraph of the statute under 35 USC 112 requires that there must be an enabling disclosure to support the breadth of the Claims, a review of the specification confirms that the scope of the various DNA sequences that are discussed above have not been enabled. In the absence of sufficient guidance, it would require undue experimentation to enable all of the sequences that are encompassed by the Claims.

Not only would it be time consuming, it would also be unpredictable to prepare all of these DNA sequences that have the activities discussed with the assurance that they will hybridize under the specified conditions.

The language of "DNA that hybridizes under moderately stringent conditions to..." literally covers all future mutations or modifications of the DNA sequences, because the claimed sequences would be expected to hybridize to all future sequences, even those not contemplated by the Applicants at the time the Invention was made.

Initially, many Inventors intended for the term "hybridize" to mean homologous DNA obtained from other species. Now, Inventors and others seek to extend the meaning to encompass minor variations and such as well. The Examiners position is consistent with the Office policy, because the Office's position has been and still is that broad claims must necessarily have broad-based enabling support and this has also been the position of several case law decisions. Further, the Examiners rejection of the Claims for non-enablement is supported by statutory requirements and is consistent with long standing case law for such issues such as In re Fisher (166 USPQ 18) and even more recent case law that are particularly on point with this rejection such as Amgen v. Chugai (18 USPQ 2d 1017).

Claims 8-10, 12-15, 17-20, 22-25 and 27 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim 12 and its dependent claims 17, 22 and 27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12, part (a) is indefinite as it is not clear how the claimed cDNA is "derived" from the coding region of a flt3-L gene (e.g. is it a portion of such, or has it been otherwise altered, e.g. by insertion, deletion or substitution of bases).

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 8-27 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent Number 5,185,438 (Lemischka). Lemischka discloses the murine flk2 receptor, and suggests cloning and isolation of the ligand to the claimed receptor. See columns 6-7 and column 12 *et*

5 *seq.*, which disclose the methods and materials to be used to obtain cDNA encoding flk2 ligands. Additionally, Lemischka teaches that the receptor may be obtained from any mammal, including human (Column 4, lines 21-24) and that the corresponding ligand "may be a growth factor that occurs naturally in a mammal, preferably the same mammal that produces the corresponding
10 receptor" (col.7:1-3). The Examiner notes that the pending claims are drawn specifically to cDNA encoding flt3 ligands; however, in view of the similarity between flk2 and flt3 (differing by only 2 amino acids in the ligand binding portion of the proteins), and further in view of the fact that the parental applications to the instant application referred to the same sequence currently claimed as encoding "flk2/flt3 ligand", the Examiner presumes, in the absence of
15 evidence to the contrary, that a flk2 ligand would also be a flt3 ligand.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to obtain cDNA encoding the flk2 ligand as suggested by Lemischka, to clone such, and to obtain the ligand proteins themselves by expressing the cloned cDNA in appropriate host cells using methods such as those taught by Lemischka. One would have been
20 motivated to do so by the disclosure of Lemischka that the ligand is useful for stimulating the proliferation of primitive mammalian hematopoietic stem cells (see Abstract). Lemischka teaches the necessary components for cloning vectors and host cells needed for cloning and expression of the ligand. With respect to those claims that recite the particular amino acid sequence encoded by the claimed DNA, it is noted that the sequence of amino acids is but one means of describing
25 the protein; it would have been obvious to clone cDNA encoding the protein as stated above; in the absence of evidence to the contrary, it is deemed to be *prima facie* obvious that the cDNA so obtained would necessarily encode such amino acid sequences.

25 Claims 8, 9, 12-14, 17-19, 22-24, 26 and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Rosnet et al. (Oncogene 6:1641) and Flanagan et al. (Cell 63:185) in view of Lemischka.

Rosnet et al. disclose cDNA encoding the murine flt3 receptor, and state that such is

5 closely related to the c-fms and c-kit receptors. Rosnet et al. disclose the desirability of obtaining the flt3 ligand at page 1648, second column. Also, it is noted that the murine flt3 disclosed by Rosnet et al. was obtained using human FMS/CSF1R as a hybridization probe (p.1641). Rosnet et al. do not disclose cDNA encoding flt3 ligand, vectors comprising such, nor recombinant production of flt3 ligand.

10 Flanagan et al. disclose a generally applicable method for the identification of an unknown ligand to a known receptor, wherein a fusion protein is constructed, consisting of the extracellular domain of the receptor fused to placental alkaline phosphatase, producing a soluble receptor affinity reagent with an enzyme tag that can be easily and sensitively traced (see abstract). Specifically, Flanagan et al. used the disclosed method to identify the ligand to the c-kit receptor.

Lemischka et al. teaches the construction of a cDNA library (i.e. insertion of cDNA into expression vectors) and use of such to clone and express a desired cDNA, see for example, column 12 line 63 to column 13, line 37.

15 It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the method disclosed by Flanagan et al. to identify the ligand to the flt3 receptor disclosed by Rosnet et al., and then to clone, express such and isolate the resulting protein using art-recognized methods as evidenced by Lemischka. One of ordinary skill in the art would have been motivated to do so by Rosnet's indication of the desirability of doing so, and would have had a reasonable expectation of success in view of the similarity between flt3 and
20 c-kit as pointed out by Rosnet. With respect to those claims that recite the particular amino acid sequence encoded by the claimed DNA, it is noted that the sequence of amino acids is but one means of describing the protein; it would have been obvious to clone cDNA encoding the protein as stated above; in the absence of evidence to the contrary, it is deemed to be *prima facie* obvious that the cDNA so obtained would necessarily encode such amino acid sequences.

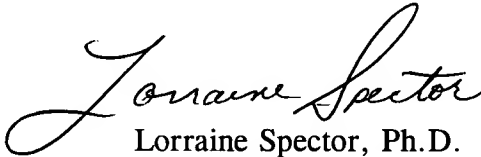
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, Ph.D. whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Garnette D. Draper, can be reached at (703)308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The Art Unit 1812 Fax Center number is (703) 308-0294. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. Please advise the Examiner at the telephone number above when a fax is being transmitted.


Lorraine Spector, Ph.D.
Patent Examiner

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